NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF OXYMETHOLONE

(CAS NO. 434-07-1)

IN F344/N RATS

AND TOXICOLOGY STUDIES OF OXYMETHOLONE IN B6C3F$_1$ MICE

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

August 1999

NTP TR 485

NIH Publication No. 99-3975

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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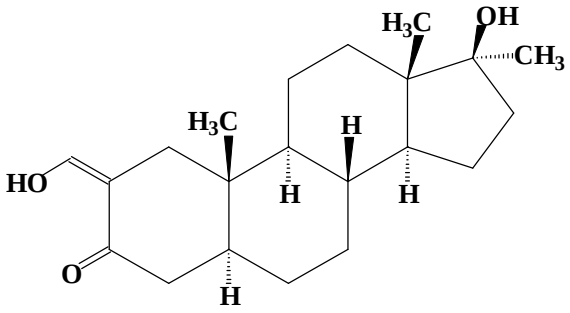
ABSTRACT



OXYMETHOLONE

CAS No. 434-07-1

Chemical Formula: $C_{21}H_{32}O_3$ Molecular Weight: 332.5

Synonyms: Adroidin; anadroyd; anasteron; anasteronal; anasterone; androstan-3-one, androstano[2,3-c]1,2,5-oxadiazol-17-ol, 17-methyl-, (5-α,17-β)-; becorel; 4,5-dihydro-2-hydroxymethylene-17-α-methyltestosterone; dynasten; HMD; 17β-hydroxy-2-(hydroxymethyl)-17-methyl-5-α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-(5-α,17-β)-; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5-α-17-β-androst-3-one; 17β-hydroxy-2-(hydroxymethylene)-17-α-methyl-5-α-androstan-3-one; 17β-hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5-α-17-β-androstan-3-one; 17β-hydroxy-2-hydroxymethylene-17α-methyl-3-androstanone; 2-hydroxymethylene-17-α-methyl-5-α-androstan-17-β-ol-3-one; 2-hydroxymethylene-17α-methyl dihydrotestosterone; 2-hydroxymethylene-17-α-methyl-17-β-hydroxy-3-androstanone; methabol; 17α-methyl-2-hydroxymethylene-17-hydroxy-5-α-androstan-3-one; oximetholonum; oximetolona; oxitosona-50; oxymethenolone; roboral; zenalosyn

Trade names: Adroyd; Anadrol; Anapolon; Anapolon 50; Nastenon; Pardroyd; Pavisoid; Plenastril; Protanabol; Synasteron

Oxymetholone is a synthetic anabolic steroid used to treat a variety of conditions, including hypogonadism and delayed puberty. It is also used to correct hereditary angioneurotic edema, manage carcinoma of the breast, promote a positive nitrogen balance following injury or surgery, and stimulate erythropoiesis. Considerable amounts of androgens are consumed by athletes in attempts to improve athletic performance. The National Institute of Environmental Health Sciences and the National Cancer Institute nominated oxymetholone for study based on its extensive illicit pharmaceutical use and the limited evidence that it is a potential human carcinogen. Male and female F344/N rats received oxymetholone (greater than 99% pure) in 0.5% methylcellulose by gavage for 16 days, 14 weeks, or 2 years, and male and female B6C3F$_1$ mice received oxymetholone in 0.5% methylcellulose by gavage for 16 days or 14 weeks. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes.

16-DAY STUDY IN RATS

Groups of five male and five female F344/N rats were administered 0, 160, 315, 625, 1,250, or 2,500 mg oxymetholone/kg body weight in 0.5% methylcellulose by gavage for 16 days. All male rats survived to the end of the study; one 2,500 mg/kg female died on day 14. The mean body weights of all dosed groups of males were significantly less than those of the vehicle controls, while those of 160 and 315 mg/kg females were significantly greater.

16-DAY STUDY IN MICE

Groups of five male and five female B6C3F$_1$ mice were administered 0, 320, 630, 1,250, 2,500, or 5,000 mg/kg in 0.5% methylcellulose by gavage for 16 days. All mice survived to the end of the study. The final mean body weights of all dosed groups of females were greater than those of the vehicle controls.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were administered 0, 80, 160, 315, 625, or 1,250 mg/kg in 0.5% methylcellulose by gavage for 14 weeks. One male rat each in the 625 and 1,250 mg/kg groups died before the end of the study. The mean body weights of males administered 160 mg/kg or greater were significantly less than those of the vehicle controls; in contrast, the mean body weights of all dosed groups of females were significantly greater.

A dose-related erythrocytosis, evidenced by increases in erythrocyte counts, total hemoglobin concentrations, and hematocrit values, occurred in dosed groups of rats at week 14. A dose-related hypocholesterolemia occurred at all time points in all dosed groups of rats. Dose- and time-related decreases in 5′-nucleotidase activity occurred in treated rats. There was a transient, treatment-related increase in the activity of alanine aminotransferase in males and females.

For male rats administered oxymetholone, cauda epididymis, epididymis, and testis weights and spermatid counts and total spermatid heads per testis were significantly less than those of the vehicle controls, and total spermatid heads per gram testis were significantly greater. Female rats in the 80 mg/kg group spent more time in diestrus and less time in estrus than did the vehicle controls.

Kidney weights of males and females and liver and uterus weights of females were increased compared to vehicle controls in rats that received 315 mg/kg or greater; thymus weights of males and females and sartorius muscle and testis weights of males were less. Compared to the vehicle controls, rats that received 160 mg/kg or greater had increased incidences of nonneoplastic lesions of the kidney and mammary gland, and the incidences of hydrometra of the uterus and dysgenesis of the ovary were increased in dosed groups of females. Female rats administered 315 mg/kg or greater had increased incidences of cytoplasmic vacuolization of the adrenal gland and myocardial degeneration of the heart. The severities of these lesions generally increased with increasing dose.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were administered 0, 160, 320, 630, 1,250, or 2,500 mg/kg in 0.5% methylcellulose by gavage for 14 weeks. All mice administered oxymetholone survived until the end of the study. The mean body weights of all dosed groups were similar to those of the vehicle controls.

The percentages of motile sperm in 1,250 and 2,500 mg/kg males were significantly less than those of the vehicle controls. The estrous cycle lengths of 630, 1,250, and 2,500 mg/kg females were significantly longer, and females in the 1,250 and 2,500 mg/kg groups spent more time in diestrus and less time in estrus.

Kidney and liver weights of males and females were greater and thymus weights of females were less than those of the vehicle controls. All dosed females had hyperplasia of the clitoral gland, metaplasia of the parietal layer epithelium of the Bowman's capsule in the kidney, and cytoplasmic alteration of the submandibular gland; these lesions were not observed in the vehicle control group. The incidences of hypoplasia of the ovary in 320 mg/kg or greater females and of parotid gland atrophy in 1,250 and 2,500 mg/kg females were increased. The results of the 14-week oral gavage studies were generally similar in rats and mice, but rats were much more sensitive to oxymetholone. Because it was not likely that a long-term mouse study would provide significant additional toxicity information, the NTP decided to conduct a 2-year study in rats only.

2-YEAR STUDY IN RATS

Groups of 90 male F344/N rats were administered 0, 3, 30, or 150 mg/kg in 0.5% methylcellulose by gavage, and 90 female F344/N rats were administered 0, 3, 30, or 100 mg/kg in 0.5% methylcellulose by

gavage for up to 104 weeks, with 9 or 10 rats per group evaluated at 3, 6, 12, or 18 months.

Survival and Body Weights

Survival of all dosed groups was similar to that of the vehicle controls. The mean body weights of the 30 mg/kg male group were generally within 10% of those of the vehicle controls, but those of the 150 mg/kg group were markedly decreased. Mean body weights of 3 and 30 mg/kg females were generally greater than those of the vehicle controls throughout the study.

Determinations of Oxymetholone in Plasma

The concentrations of oxymetholone in plasma of male and female rats receiving 3 mg/kg for 6, 12, or 18 months were generally below the limits of quantification; therefore, all plasma concentrations in the 3 mg/kg group are considered to be estimates (Table 8). The plasma concentrations at 30 mg/kg were approximately one order of magnitude greater than those of the estimates for males and females receiving 3 mg/kg. There were no dose-related differences in plasma concentrations in female rats receiving 30 or 100 mg/kg, but plasma concentrations in males were significantly elevated in the 150 mg/kg group. It was concluded that oxymetholone kinetics was saturated at 30 mg/kg in female but not male rats.

Pathology Findings

A wide spectrum of neoplasms and nonneoplastic lesions was seen in rats administered oxymetholone for 2 years. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in 100 mg/kg females as were the incidences of basophilic and clear cell foci in 150 mg/kg males and 100 mg/kg females compared to vehicle controls. The incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) were significantly increased in 30 mg/kg females. The incidences of mineralization in the lung of 150 mg/kg males and 30 and 100 mg/kg females were significantly increased. The incidence of keratoacanthoma was increased in 30 mg/kg females, and the combined incidence of squamous cell papilloma, keratoacanthoma, basal cell adenoma, squamous cell carcinoma, or carcinoma of the sweat gland was significantly increased in 100 mg/kg females. The incidences of subcutaneous tissue fibroma and fibroma or fibrosarcoma (combined) were significantly increased in 3 mg/kg males.

At 2 years, the incidences of benign pheochromocytoma and benign or malignant pheochromocytoma (combined) of the adrenal gland in 150 mg/kg males and medullary hyperplasia in 100 mg/kg females were significantly increased. The incidences of cytoplasmic vacuolization of adrenal cortical cells were significantly increased in 30 and 150 mg/kg males at 18 months and 2 years and in 100 mg/kg females beginning at 12 months and in 30 mg/kg females at 2 years.

The incidences of renal tubule adenoma in 3 and 150 mg/kg males were slightly increased. An extended evaluation of the kidney was conducted, and additional incidences of renal tubule adenoma were observed in step sections in vehicle control and dosed male rats. The combined single- and step-section incidence of renal tubule adenoma was significantly increased in 3 mg/kg males. The incidences of nephropathy were significantly increased in 30 and 150 mg/kg males at 2 years and in 100 mg/kg females beginning at 3 months. The severities of nephropathy were significantly increased in dosed groups of males at 2 years and in 100 mg/kg females at 18 months and 2 years. The incidences of mineralization of the kidney were significantly increased in 150 mg/kg males at all time points.

The incidences of ovarian dysgenesis were significantly increased in 100 mg/kg females beginning at 3 months and in 30 mg/kg females beginning at 6 months, and severities increased with increasing dose. The incidences of chronic myocardial degeneration (cardiomyopathy) were significantly increased in 100 mg/kg females at 6 months and 2 years and the severity was increased at 2 years. The incidences of lobular hyperplasia were increased in 150 mg/kg males at 18 months and 2 years and in 30 and 100 mg/kg females at all time points. The incidences of seminiferous tubule degeneration were significantly increased in 30 and 150 mg/kg males at 2 years, and the incidences of mineralization of the testis were increased in 150 mg/kg males at 12 months and in 30 mg/kg males at 18 months and at 2 years.

Decreased incidences of neoplasms occurred in male and female rats. The incidence of uterine stromal polyp or stromal sarcoma (combined) was significantly decreased in 100 mg/kg females at 2 years. The incidences of mammary gland fibroadenoma and fibroadenoma or carcinoma (combined) were significantly decreased in all dosed groups of females. The incidences of pituitary gland pars distalis adenoma were significantly decreased in 30 and 100 mg/kg females at 2 years. The incidences of testicular interstitial cell adenoma were significantly decreased in 30 and 150 mg/kg males at 18 months and in all dosed groups at 12 months and 2 years. The incidences of mononuclear cell leukemia were significantly decreased in 30 and 150 mg/kg males and 100 mg/kg females at 2 years.

GENETIC TOXICOLOGY

Oxymetholone was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation. It did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9, and no increase in the frequency of micronucleated normochromatic erythrocytes was noted in peripheral blood samples from male or female mice treated for 14 weeks with oxymetholone.

CONCLUSIONS

Under the conditions of this 2-year gavage study, there was *equivocal evidence of carcinogenic activity** of oxymetholone in male F344/N rats based on increased incidences of subcutaneous tissue fibromas and fibromas or fibrosarcomas (combined) of the skin, variably increased incidences of benign and benign or malignant pheochromocytomas (combined) of the adrenal gland, and increased incidences of renal tubule adenomas. There was *clear evidence of carcinogenic activity* of oxymetholone in female F344/N rats based on increased incidences of hepatocellular neoplasms. Increased incidences of alveolar/bronchiolar neoplasms and skin neoplasms in female rats were also related to oxymetholone administration.

Decreased incidences of alveolar/bronchiolar neoplasms and testicular interstitial cell adenomas in males; uterine stromal polyps or stromal sarcomas (combined), mammary gland neoplasms, and pituitary gland pars distalis adenomas in females; and mononuclear cell leukemia in males and females were related to oxymetholone administration.

In addition, gavage administration of oxymetholone to male and female F344/N rats resulted in a spectrum of nonneoplastic effects frequently reported with administration of synthetic anabolic androgens.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Oxymetholone

	Male F344/N Rats	Female F344/N Rats
Doses in methylcellulose by gavage	0, 3, 30, and 150 mg/kg	0, 3, 30, and 100 mg/kg
Body weights	150 mg/kg group less than the vehicle control group	3 and 30 mg/kg groups generally greater than the vehicle control group
Survival rates	15/51, 15/50, 14/50, 20/50	25/50, 29/50, 30/50, 31/50
Nonneoplastic effects	Liver: basophilic focus (23/51, 29/50, 41/50, 38/49); clear cell focus (2/51, 2/50, 6/50, 12/49) Lung: mineralization (19/51, 25/50, 27/50, 28/47) Adrenal gland: cortex, cytoplasmic vacuolization (22/51, 23/50, 40/50, 33/49) Kidney: mineralization (6/51, 6/50, 9/50, 25/49); nephropathy (43/51, 47/50, 50/50, 48/49); severity of nephropathy (2.0, 2.6, 2.7, 2.7) Mammary gland: lobular hyperplasia (0/51, 0/48, 4/49, 35/50) Testes: degeneration (9/51, 9/50, 37/50, 28/49); mineralization (17/51, 10/50, 33/50, 19/49)	Liver: basophilic focus (39/50, 40/50, 37/50, 41/49); clear cell focus (5/50, 11/50, 6/50, 14/49) Lung: mineralization (15/50, 23/50, 33/50, 33/49) Adrenal gland: cortex, cytoplasmic vacuolization (4/50, 5/50, 21/50, 37/49) Kidney: nephropathy (32/50, 26/50, 38/50, 41/49); severity of nephropathy (1.3, 1.2, 1.2, 1.7) Ovary: dysgenesis (0/50, 1/49, 43/50, 49/49); severity of dysgenesis (, 1.0, 2.7, 3.4) Heart: myocardium, chronic degeneration (29/50, 34/50, 40/50, 45/49); severity of degeneration (1.3, 1.3, 1.8, 1.8)
Neoplastic effects	None	Liver: hepatocellular adenoma (1/50, 1/50, 1/50, 8/49); hepatocellular adenoma or carcinoma (1/50, 1/50, 1/50, 10/49) Lung: alveolar/bronchiolar adenoma (0/50, 0/50, 6/50, 1/49); alveolar/bronchiolar adenoma or carcinoma (0/50, 0/50, 7/50, 1/49) Skin: squamous cell papilloma, keratoacanthoma, basal cell adenoma, squamous cell carcinoma, or carcinoma (0/50, 0/50, 4/50, 5/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Oxymetholone

	Male F344/N Rats	Female F344/N Rats
Uncertain Findings	Skin: subcutaneous tissue, fibroma (0/51, 5/50, 2/50, 2/50); subcutaneous tissue, fibroma or fibrosarcoma (0/51, 7/50, 2/50, 2/50) Adrenal gland: benign pheochromocytoma (19/51, 21/50, 21/50, 29/49); benign or malignant pheochromocytoma (19/51, 25/50, 21/50, 29/49) Kidney: renal tubule adenoma (standard evaluation - 0/51, 1/50, 0/50, 2/49; standard and extended evaluations combined - 4/51, 13/50, 1/50, 6/49)	None
Decreased incidences	Testes: adenoma (33/51, 20/50, 0/50, 0/49) Mononuclear cell leukemia: (21/51, 15/50, 7/50, 4/50)	Uterus: stromal polyp or stromal sarcoma (5/50, 9/50, 2/50, 0/50) Mammary gland: fibroadenoma (21/50, 11/50, 1/50, 4/50); fibroadenoma or carcinoma (23/50, 11/50, 1/50, 4/50) Pituitary gland (pars distalis): adenoma (27/50, 26/50, 18/49, 14/50) Mononuclear cell leukemia: (12/50, 11/50, 11/50, 5/50)
Level of evidence of carcinogenic activity	Equivocal evidence	Clear evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated normochromatic erythrocytes	
Mouse peripheral blood *in vivo*:	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on oxymetholone on 30 October 1998 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 30 October 1998, the draft Technical Report on the toxicology and carcinogenesis studies of oxymetholone received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. W.C. Eastin, NIEHS, introduced the toxicology and carcinogenesis studies of oxymetholone by discussing the uses of the chemical and the rationale for the study, describing the experimental design in rats, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in male and female rats. Dr. Eastin also discussed the 16-day and 14-week studies in male and female B6C3F$_1$ mice. The proposed conclusions for the 2-year study were *equivocal evidence of carcinogenic activity* in male F344/N rats and *clear evidence of carcinogenic activity* in female F344/N rats.

Dr. Fischer, a principal reviewer, was unable to attend the meeting but had submitted her review, which Dr. L.G. Hart, NIEHS, read into the record. Dr. Fischer agreed with the proposed conclusions. She thought the comparison of the rodent results with studies in humans was thorough and enhanced confidence in the conclusions. Dr. Fischer questioned whether the increased incidence of lung neoplasms in the 30 mg/kg group of females should be considered treatment related when there was no significant increase in these neoplasms in the 100 mg/kg group.

Dr. Bailer, the second principal reviewer, agreed with the proposed conclusions. He wondered if all rat data, including interim sacrifice data, should be routinely included in tests of tumorigenic trends. Dr. J.K. Haseman, NIEHS, responded that while statistical analyses that include the interim sacrifice data are done, they are usually not included in the report unless they affect the overall interpretation of the data. In addition, neoplasms are seldom observed at interim sacrifices. Dr. Bailer noted the statement that "there is a strong correlation between a chemical's electrophilicity, mutagenicity in *Salmonella*, and carcinogenicity in rodents" and wondered whether that is true for all chemical classes. Dr. Eastin said that point would be clarified and the statement would be modified if necessary.

Dr. Cullen, the third principal reviewer, agreed in principle with the proposed conclusions. He thought the lack of a dose-related response for hepatocellular neoplasms in female rats suggested *some evidence* rather than *clear evidence* of carcinogenic activity. Dr. Eastin commented that interpretation of neoplasm results is difficult with synthetic anabolic steroid analogues of testosterone, which has complicated and divergent biological effects. The conclusion for liver neoplasms was based on the rarity of these neoplasms, especially carcinomas, in female rats. Dr. Bailer observed that he would not say there is no dose response but rather that there is not a linear dose response. Dr. Cullen said that given the International Agency for Research on Cancer statement that there is limited evidence of human carcinogenicity for anabolic compounds and the paucity of data on carcinogenicity of oxymetholone in animals, it would have been useful to have more information on mice, and especially for mouse liver.

Dr. Bailer moved that the Technical Report on oxymetholone be accepted with the revisions discussed and the conclusions as written for male rats, *equivocal evidence of carcinogenic activity*, and for female rats, *clear evidence of carcinogenic activity*. Dr. Hecht seconded the motion. Dr. Cullen said that based on the definition of *clear evidence* and the lack of a clear dose response, he would offer an amendment to change the conclusion in female rats to *some evidence of carcinogenic activity*. Lacking a second, that amendment was tabled. Dr. Bailer's original motion was accepted with four yes votes to one no vote (Dr. Cullen).